

Investigation of the D188V mutation in the SCN1A gene in patients with idiopathic generalized epilepsy

 Hatice Seğmen¹,  Osman Tanık²

¹Department of Neurology, İstanbul Kanuni Sultan Süleyman Training and Research Hospital, University of Health Sciences, İstanbul, Türkiye

²Department of Neurology, Apex Medical Center, İstanbul, Türkiye

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ABSTRACT

Aims: This study aims to investigate the D188V mutation on the sodium channel protein type 1 subunit alpha (SCN1A) in selected patients with idiopathic generalized epilepsy (IGE). The mutation in the SCN1A gene is the most common gene mutation in ion channels and is believed to play an important role in the pathology of IGE.

Methods: This study included patients with IGE selected among patients with epilepsy admitted to the outpatient neurology department of Okmeydanı Training and Research Hospital. Medical history, clinical examination, electroencephalography (EEG), and imaging features of the patients were evaluated. IGE patients with no etiological cause were included in the study. The D188V mutation on the SCN1A gene was investigated by PCR method in the blood samples of the patients.

Results: D188V mutation on the SCN1A gene was investigated in a total of 65 patients, of which 31 were females and 34 were males. None of the cases had a D188V mutation on the SCN1A gene.

Conclusion: Increasing genetic research is promising to elucidate the etiology of many diseases. However, these studies require persistent repetition since they are complex and difficult. The role of genetics in elucidating the etiology of epilepsy is undisputed. Although existing studies support the genetic basis, further studies are still needed.

Keywords: Idiopathic generalized epilepsy, genetics, sodium channel, mutation

INTRODUCTION

Epilepsy is one of the most common neurological disorders, affecting approximately 1% of the general population.¹ Elucidation of the etiology of such a common disease has long occupied the scientific community, and the first problem encountered in this regard was the etiologic heterogeneity. Although there are many causes of epilepsy, the exact etiology cannot be identified in most cases. These cases with unidentified etiology are now classified as idiopathic. There is no informational medical history, familial findings, or clinical and laboratory findings to indicate the etiology. It is widely accepted that genetic factors contribute to the etiology of these idiopathic epilepsies, which account for 40% of all epilepsy cases.

Recent studies have focused attention on genetics by identifying the pathophysiology of several epileptic syndromes such as Benign Familial Neonatal Seizures (BFNS), Benign Familial Infantile Seizures (BFIS), Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE), and Autosomal Dominant Lateral Temporal Epilepsy (ADLTE). However, a suspect gene has only been identified in a very small number of epilepsies believed to be hereditary. These

are the genes that code ion channels or functional proteins. Most syndromes of epilepsy show complex rather than simple inheritance. Therefore, the presence of genetic diversity and the challenges in determining the exact phenotype have complicated the search for candidate genes associated with these diseases. These genes can play a crucial role in understanding the causes of epilepsy and facilitate accurate diagnosis. They may help clinicians both in the treatment of seizures and in the prevention of epileptogenesis.

METHODS

The study was carried out with the permission of Ethical Committee of Okmeydanı Training and Research Hospital (Date: 12.01.2004, Decision No: 19-04). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. A total of 65 patients with IGE who were admitted to the outpatient clinic of the Neurology Department of Okmeydanı Training and Research Hospital in 2004-2005 and who had no etiological cause based on history, EEG, and imaging features were prospectively analyzed. Of these patients, 31 were female and

34 were male; 44 had their first epileptic seizure before the age of 16, while 21 had their first seizure at age 16 or older. Each of these admitted patient's personal medical history, family history, clinical progression, seizure attributes, medication and treatment records, neurological examination results, and imaging findings (including EEG, CT, and MRI scans) were meticulously analyzed, alongside laboratory findings such as hemogram, biochemistry, and antiepileptic drug blood levels. The patients were followed up for one year. A family tree was constructed for all patients, and consanguineous marriages and the presence of other family members with epilepsy were investigated.

Ten cc of venous blood with EDTA was collected from all patients with the consent of themselves or their first-degree relatives. These blood samples were taken to the Experimental Medicine Research Institute of Istanbul University (DETAE) for genetic research. Genomic DNA was extracted from peripheral blood lymphocytes of the members in the IGE patients. The coding region of the SCN1A gene were screened for mutation using polymerase chain reaction (PCR) method.

RESULTS

The study was conducted at the Neurology Department of the Ministry of Health Okmeydanı Training and Research Hospital between 2004 and 2005, involving a total of 65 patients, comprising 31 females (47.7%) and 34 males (52.3%) (Table 1).

The most common seizure type in both men and women is generalized tonic-clonic seizures (GTC). GTC was present in 54.8% of females and 76.5% of males (Table 2). A total of 8 females had the syndrome, of which 3 had generalized epilepsy with febrile seizures plus (GEFS+) (37.5%), 3 had generalized myoclonic epilepsy (GME) (37.5%), and 2 had childhood absence epilepsy (CAE) (25%). A total of 7 males had the syndrome, 4 with GEFS+ (57.1%), 2 with GME (28.6%), and 1 with CAE (14.3%) (Table 3). While GTC was observed in 61.4% of patients who had their first seizure at age 16 years or younger, the rate of GTC was 76.2% in patients whose age at first seizure was older than 16 years (Table 4). There was no statistically significant relationship between age at first seizure and medical history ($p>0.05$). No statistically significant relationship was found between age at first seizure and treatment response ($p>0.05$). It was observed that response to treatment was mostly seizure-free in patients both under and over 16 years of age, followed by a resistant response. No statistically significant relationship was found between age at first seizure and consanguineous marriage ($p>0.05$). Consanguineous marriages were found in 38.6% of patients younger than 16 years and 23.8% of patients 16 years and older. There was no statistically significant relationship between age at first seizure and the presence of other epileptic relatives ($p>0.05$) (Table 5). Among cases with a first seizure onset before the age of 16, 56.8% have a family history, compared with 66.7% of cases with a first seizure onset at age 16 or older. No statistically significant relationship was found between the presence of epilepsy among family members and medical history ($p>0.05$). There was no statistically significant relationship between the presence of family history and treatment response ($p>0.05$). The response to treatment was mostly seizure-free in patients with and without family history, followed by a resistant response. There was no

statistically significant relationship between the presence of epilepsy in the history and clinical photosensitivity ($p>0.05$) (Table 6).

Table 1. Frequency table

		n	%
Gender	Female	31	47.7
	Male	34	52.3
Age at first seizure	≤ 16	44	67.7
	> 16	21	32.3
Syndrome type	GEFS+	7	46.7
	GME	5	33.3
History	CAE	3	20.0
	Have had FS	11	16.9
Seizure type	Have not had FS	54	83.1
	Ato-Myo	3	4.6
Clinical photosensitivity	GTC	43	66.2
	GTC-Abs	3	4.6
Treatment response	Myo-GTC	5	7.7
	GTC-CP	1	1.5
Consanguineous marriage	Myo	2	3.1
	Abs	2	3.1
Another family member with epilepsy	Tonic	3	4.6
	Ato-GTC	1	1.5
Seizure type	Tonic-Ato-GTC	1	1.5
	Ato	1	1.5
Clinical photosensitivity	Yes	5	7.7
	No	60	92.3
Treatment response	Seizure free	35	56.5
	Resistant	19	30.6
Consanguineous marriage	Decrease	8	12.9
	Yes	22	33.8
Another family member with epilepsy	No	43	66.2
	Yes	39	60.0
Consanguineous marriage	No	26	40.0
	Yes	39	60.0

GEFS+: Generalized epilepsy with febrile seizures plus, GTC: Generalized tonic clonic, GME: Generalized myoclonic epilepsy, CAE: Childhood absence epilepsy, FS: Febrile seizure, Ato-Myo: Atonic myoclonic, GTC-Abs: generalized tonic clonic-absence, Myo-GTC: Myoclonic-generalized tonic clonic, GTC-CP: Generalized tonic clonic-complex partial, Myo: Myoclonic, Abs: absence, Ato-GTC: Atonic-generalized tonic clonic, Tonic-Ato-GTC: Tonic-atonic-generalized tonic clonic, Ato: Atonic.

Table 2. Seizure type distribution by gender

		Female		Male	
		n	%	n	%
Seizure Type	Ato-Myo	3	9.7	-	-
	GTC	17	54.8	26	76.5
	GTC-Abs	2	6.5	1	2.9
	Myo-GTC	3	9.7	2	5.9
	GTC-CP	-	-	1	2.9
	Myo	2	6.5	-	-
	Abs	1	3.2	1	2.9
	Tonic	3	9.7	-	-
	Ato-GTC	-	-	1	2.9
	Tonic-Ato-GTC	-	-	1	2.9
Total	Ato	-	-	1	2.9
		31	100.0	34	100.0

Ato-Myo: Atonic-myoclonic, GTC: Generalized tonic clonic, GTC-Abs: generalized tonic clonic-absence, Myo-GTC: Myoclonic-generalized tonic clonic, GTC-CP: Generalized tonic clonic-complex partial, Myo: myoclonic, Abs: Absence, Ato-GTC: Atonic-generalized tonic clonic, Tonic-Ato-GTC: Tonic-atonic-generalized tonic clonic, Ato: atonic.

Table 3. Distribution of syndrome type by gender

Syndrome Type		Female		Male	
		n	%	n	%
Syndrome Type	GEFS+	3	37.5	4	57.1
	GME	3	37.5	2	28.6
	CAE	2	25.0	1	14.3
Total		8	100.0	7	100.0

GEFS+: Generalized epilepsy with febrile sizers plus, GTC: generalized tonic clonic, GME: generalized myoclonic epilepsy, CAE: childhood absence epilepsy

Table 4. Distribution of seizure types by age at first seizure

Seizure Type		Age at First Seizure			
		≤ 16		> 16	
		n	%	n	%
Seizure Type	Ato-Myo	2	4.5	1	4.8
	GTC	27	61.4	16	76.2
	GTC-Abs	2	4.5	1	4.8
	Myo-GTC	4	9.1	1	4.8
	GTC-KP	-	-	1	4.8
	Myo	2	4.5	-	-
	Abs	2	4.5	-	-
	Tonic	3	6.8	-	-
	Ato-GTC	1	2.3	-	-
	Tonic-Ato-GTC	1	2.3	-	-
	Ato	-	-	1	4.8
Total		44	100.0	21	100.0

Ato-Myo: Atonic myoclonic, GTC-Abs: Generalized tonic clonic-absence, Myo-GTC: Myoclonic-generalized tonic clonic, GTC-KP: Generalized tonic clonic-complex partial, Myo: Myoclonic, Abs: Absence, Ato-GTC: Atonic-generalized tonic clonic, Tonic-Ato-GTC: Tonic-atonic-generalized tonic clonic, Ato: Atonic.

Table 5. Comparisons by age at first seizure

		Age at First Seizure				
		≤ 16		> 16		p
		n	%	n	%	
History	Have had FS	7	15.9	4	19.0	0.752
	Have not had FS	37	84.1	17	81.0	
Treatment Response	Seizure free	23	54.8	12	60.0	0.877
	Resistant	13	31.0	6	30.0	
	Decrease	6	14.3	2	10.0	
Consanguineous Marriage	Yes	17	38.6	5	23.8	0.237
	No	27	61.4	16	76.2	
Other Epileptic	Yes	25	56.8	14	66.7	0.448
	No	19	43.2	7	33.3	
FS:febrile seizure						

Table 6. Comparisons by presence of family history

		Other epileptic family members				
		Yes		No		p
		n	%	n	%	
History	Have had FS	8	20.5	3	11.5	0.344
	Have not had FS	31	79.5	23	88.5	
Treatment Response	Seizure free	19	52.8	16	61.5	0.534
	Resistant	13	36.1	6	23.1	
	Decrease	4	11.1	4	15.4	
Clinical Photosensitivity	Yes	3	7.7	2	7.7	1.000
	No	36	92.3	24	92.3	
FS:febrile seizure						

Genetic Analysis

D188V mutation on the SCN1A gene was investigated in 65 patients, of which 31 were females and 34 were males. The D188V mutation on the SCN1A gene was not detected in any of the cases, including those with familial characteristics and those fitting a syndrome type in which this mutation can be found.

Statistics Analysis

SPSS (Statistical Package for Social Sciences) for Windows 10.0 software was used for statistical analysis of the findings obtained in the study. In addition to descriptive statistical methods (frequencies), the chi-square test and Fisher exact chi-square test were used to compare qualitative data in the study. The results were assessed with a 95% confidence interval and significance was determined at the $p < 0.05$ level.

DISCUSSION

Many studies have been conducted to explain the etiology of IGE. Genetic studies are the most interesting among these studies. Genetic studies have demonstrated the role of ion channels in the pathophysiology of IGE. Rare epilepsy syndromes with monogenic inheritance have been associated with mutations in genes encoding subtypes of voltage-gated (sodium, potassium, chloride channels) and ligand-gated ion channels.^{2,3} The long-standing focus of antiepileptic drugs on sodium channels has led genetic research to shift in this direction. Sodium channels are composed of pore alpha and regulatory beta subtypes, and specific mutations in these channels cause epilepsy syndromes ranging from benign, self-limiting conditions such as febrile seizures to severe epilepsies causing intractable seizures and intellectual loss.⁴ Mutations in the genes encoding voltage-gated sodium channels cause a variety of epilepsy syndromes in humans, with most of the mutations occurring SCN1A. The present study investigates the D188V mutation in the SCN1A gene, which is one of the genetically inherited sodium channel pathologies that have a marked importance in the etiology of epilepsy. Regarding the etiology of epilepsy, several genetic studies have been conducted on channel pathologies. If we look at some of these studies, Patrick Cossette et al.⁵ showed the D188V mutation in the SCN1A gene in a large family with GEFS+. Laura Saez-Hernandez et al. found a point break translocation in the 6p21 gene encoding potassium channels in a family with IGE.⁶ In their study, Iori Ohmori et al.⁷ showed SCN1A mutation in 24 of 29 patients with infantile myoclonic epilepsy (IME). J. Spampinato et al.⁸ found a W1204R mutation in the SCN1A gene in their study of patients with GEFS. Ching Chou et al. found no association between SCN1A polymorphism and FS in their study of families with febrile seizures (FS).⁹ In their study, N. Pineda-Trujillo et al. found a mutation in the SCN1A gene in a large South American family with GEFS+.¹⁰ M. Ito et al. showed the presence of a missense mutation in the SCN1A gene in 2 families with GEFS+.¹¹ A large number of SCN1A missense mutations have also been identified in Dravet Syndrome (DS) patients. It is likely that many of these abolish channel function, possibly by altering the properties of the channel, trafficking or subcellular localization, or interactions with other molecules. Unlike GEFS+ mutations that segregate within affected families, most DS mutations are de novo in the affected child.¹² Xu XJ et al.¹³ showed SCN1A

gene mutations in 4 of 39 families with GEFS+. de Lange IM et al. investigated 87 patients with SCN1A-related epilepsy. But they could not fully explain the variable phenotypes caused by similar pathogenic SCN1A mutations.¹⁴ This study, conducted on a large cohort of individuals with IGE, aimed to explore the role of genetics in the etiology of epilepsy in Türkiye and the significance of channel pathologies in its etiology. In our genetic study involving 65 patients with IGE, no correlation was found between IGE and the D188V mutation on the SCN1A gene.

In epilepsy genetics research, it has been proposed that the heterogeneity in etiology may be due to genetic heterogeneity, with a wide array of genes potentially contributing to epilepsy. It has been suggested that epilepsy may originate from different genes within different families and that a single genetic factor may manifest in different clinical presentations in different individuals. Since many factors influence the correspondence between genotype and phenotype, it is difficult to identify epilepsy genes. Pathology in a single gene or a single mutation can cause disease with different phenotypes, and pathology in different genes can cause the disease with the same phenotype. Some epilepsies may have a stronger genetic ground than others. Even among genetically identified epilepsies, the genes responsible may vary. The absence of mutation in our study may be due to the genetic heterogeneity in the etiology of epilepsy. However, the inclusion of numerous subtypes of IGE in the selected group, indicating insufficient homogeneity, coupled with the small sample size, may also have influenced this result.

Despite the considerable interest in this topic in Turkey, current conditions restrict studies to the detection of known genes and chromosomal abnormalities. Considering that the disease genes that cause epilepsy may be different even within the same family, the genes that cause the disease in our society may also be different from other societies. Considering these differences in disease genes between societies, it is clear that further studies are needed to determine the genetic profile of epilepsy in the Turkish population.

There is a risk of IGE in relatives of groups with IGE. Studies have shown that this risk is associated with age at the onset of epilepsy. The risk of developing epilepsy in relatives of individuals aged 35 years and older with IGE is not elevated compared to the general population. Therefore, it is more accurate to refrain from seeking a genetic basis for epilepsies that manifest after the age of 35.¹⁵

In their study, Eisner et al. found a remarkable familial tendency for epilepsy within groups whose seizures began before the age of 16.¹⁶ On the other hand, W. G. Lennox showed that the incidence of epilepsy was high in relatives of patients with early-onset seizures.¹⁷ In our study, the presence of family history was higher in patients with a first seizure age of 16 years and below than in those with a first seizure age of 16 years and above. However, no statistically significant correlation was found between medical history, response to treatment, consanguinity, and presence of other epileptic family members in those with age of first seizure 16 years or less compared with those with age of first seizure 16 years or more ($P>0.05$).

Similar to epilepsy, FS is heterogeneous and it is difficult to assess familial risks. The risk of these seizures increases in the children, siblings, and nephews of those who have experienced seizures. In population-based studies, the risk in siblings ranges between 6% and 20%.^{18,19}

In our study, the rate of family history was high in patients with FS. However, the rate of having FS was not found to be statistically significant in patients with a positive family history compared to those without a positive family history ($p>0.05$).

CONCLUSION

The role of genetics in elucidating the etiology of epilepsy is undisputed. Although some studies support a genetic basis, further studies are still needed on this subject. Increasing genetic research promises a bright future in elucidating the etiology of many diseases. However, the complexity and difficulty of such studies require patience and persistent repetition. In this study, only the D188V mutation on the SCN1A gene was investigated in patients with IGE. The absence of this mutation in our study does not mean that there are no other genetic mutations in the etiology of IGE. The role of genetics in the etiology of epilepsy should be further studied in larger, more homogeneous, and more specific subgroups and on different genes.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ethical Committee of Faculty of Okmeydanı Training and Research Hospital (Date: 12.01.2004, Decision No: 19-04).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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